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Hypertension and Nutrition:

Fat-soluble Vitamins A, D and E

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Table of Content

ABSTRACT

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Arterial hypertension (AH) is a disease affecting population globally, and thus considered as a problem of public health and socioeconomic. Studies are trying to identify the connection between diet and the prevalence of arterial hypertension.

Objective of the study was to determine possible association between an occurrence of AH and fat-soluble vitamins A, D and E intake.

The nested, case-control population study investigation was grounded on database from the Spanish Hortega study, and performed on a random sample of 1,514 people (50.3 % women, 49.7 % men). From this sample we selected those aged ≥ 40 years old and untreated for hypertension and divided them into two groups: non-hypertensive (n = 429; 63.6 %) (controls), and newly diagnosed AH (n = 246; 36.4 %) (cases). Biochemical and anthropometric measurements, data on dietary intakes, education, socioeconomic status, place of residence, health habits, comorbidities, consumption of alcohol and tobacco were used for our study. Descriptive study of the data was carried out and compared by ANOVA and Chi-Square; analytical study was performed through logistic regression, calculating odds ratio and a set of adjusted models with different variables. No p value higher than 0.05 was considered significant.

The results showed higher intake of vitamin A in AH subpopulation (1732,77 ± 962,27 μg vs. 1655,89 ± 902,81 μg), and intakes of vitamins D and E were lower (8,13 ± 9,71 μg vs. 8,25 ± 9,52 μg and 18,79 ± 7,84 mg vs. 18,60 ± 8,20 mg, respectively), but with no statistically significant differences, neither in any of adjusted models.

This study did not identify any association between the intake of fat-soluble vitamins A, D, E and AH occurrence in any of investigated cases.

Keywords: fat-soluble vitamins, arterial hypertension, nutrition.

ABSTRAKT

Hypertension and nutrition: Fat-soluble vitamins A, D and E

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Arteriální hypertenze je nemoc, postihující lidstvo celosvětově, a proto je považována nejen za problém zdravotnický, ale také socioekonomický. Studie se proto snaží identifikovat spojení mezi potravou a prevalencí hypertenze.

Cílem studie bylo určit, zda-li příjem lipo-solubilních vitamin A, D a E ovlivňuje výskyt arteriální hypertenze.

Výzkum byl založen na výsledcích projektu Hortega a proveden na náhodném vzorku 1 514 jedinců ve věku 21 až 89 let, z nichž 50.3 % byly ženy a 49.7% muži. Vzorek byl rozdělen na dvě skupiny. S normálním tlakem, starší 40-ti let (n = 429; 28.3 %) a hypertonici starší 40 let.(n = 246;16.2 %). Biochemické a antropometrické vyšetření byly provedeny za užití standardních postupů.Příjmy živin byly odhadnuty za použití validovaných dotazníků, dosažené vzdělání, socioekonomický status, bydliště, zdravotní návyky, konzumace alkoholu, kouření a existence komorbitit byla vzata v úvahu. Získaná data byla porovnána pomocí ANOVA a Chi-squre, analýza závislosti a korelace byla provedena skrze multivariantní regresi pro předpovězení a vyhodnocení příjmu vitaminů a přítomnosti AH. P hodnoty vyšší než 0,05 nebyly brány v úvahu jako statisticky rozdílné.

Výsledky ukázaly, že příjem vitaminu A byl vyšší v hypertenzní subpopulaci (1732,77 ± 962,27 μg vs. 1655,89 ± 902,81 μg) a příjem vitaminů D a E byl nižší (8,13 ± 9,71 μg vs. 8,25 ± 9,52 μg and 18,79 ± 7,84 mg vs. 18,60 ± 8,20 mg, respective). Avšak rozdíly nebyly statisticky významné a to ani v žádném z vytvořených modelů.

Naše studie nenašla vztah mezi příjmem liposolubilních vitaminů A.D, E a výskytem arteriální hypertenze.

Klíčová slova: vitamin rozpustné v tucích, arteriální hypertenze, výživa.

1. Introduction

Arterial hypertension (AHT) today represents a significant public health problem in developed countries. Together with hypercholesterolemia and smoking, they represent major cardiovascular risk factors whose high prevalence and ability to be modified by therapeutic intervention and changes in lifestyle make it an issue of great interest of public health and socioeconomic (Banegas, 2002).

It has been assumed that a good control of AHT could prevent much of the cardiovascular diseases and that the two pillars of the monitoring are certainly adequate detection and optimal fulfilment of prescribed treatment using the latest methods and medication, together with optimizing lifestyle resulting in better controlled AHT.

Lack of control of blood pressure (BP) may consequently occur in increased incidence of hospitalization and mortality from cardiovascular disease, various kidney diseases, cerebral and heart failure, decreasing of quality of life along with increased dependence, resulting together in increased health and social services costs.

1.1 Prevalence of hypertension

The prevalence of AHT in Spain (Banegas, 2002; Banegas, Graziani, 2005) is approximately 35% (Table 1.) (Banegas et al., 2002; Banegas et al., 1998), particularly 40% in people aged 35-65 years, and even more than 60% in those over 60 years old, defined as AHT if BP values are higher than 140 / 90 (Table 2). This prevalence will, according to contemporary trends, affect 29 % of the global adult population in 2025 (Coca Payeras, 2003).

The evolution of the degree of control of AHT has been remarkable increased as observed in studies „Control press" carried out amongst the AHT population diagnosed in primary care and treated with drugs in Spain between 1994 and 2003 (Table 1) (Coca Payeras, 2003).

Overall, the data obtained in this study represents a threefold increase regarding AHT control in the early nineties.

Table 1 Prevalence, awareness, treatment and control of hypertension in adults in Spain between 1980 and 2002.

	1980	1990	1998	2002
Prevalence (SBP/ DBP ≥140/90 mmHg)	30%	35%	35%	35%
Diagnosed hypertension	40%	50%	60%	65%
Treated diagnosed hypertension	40%	72%	78%	85%
Treated hypertension in total	16%	36%	50%	55%
Controlled hypertension	10%	13%	16%	25%
Controlled diagnosed hypertension	4%	9%	13%	21%
Hypertension controlled in total	2%	5%	8%	14%

The treatment refers to the antihypertensive drug therapy. SBP: systolic blood pressure, DBP: diastolic blood pressure. Taken from Banegas JR, Graziani A. 2005.

Table 2 Distribution of blood pressure levels and arterial hypertension in Spain according to age

	Normotension or controlled hypertension			Hypertension		
	Optimal	Normal	High normal	Grade 1	Grade 2	Grade 3
SBP mmHg	<120	120-129	130-139	140-159	160-179	≥180
DBP mmHg	<80	80-84	85-89	90-99	100-109	≥110
Prevalence in people aged 35-65 years	23%	17%	17%	28%	11%	4%
Prevalence in people aged over 60 years	10%	14%	20%	36%	15%	5%

SBP: systolic blood pressure; DBP: diastolic blood pressure.
Taken from Banegas JR, Graziani A. 2005.

In the international context, the prevalence of AHT in Spanish adults and other European countries is higher (41%) than in countries like United States of America (USA)

and Canada (27%) (Banegas, 2002). Although these differences might not seem minor, in the same time, according to data obtained from National surveys of these countries, adults over 60 have almost the same prevalence (Table 3.) (Banegas JR, Rodríguez Artalejo, 2002, Banegas et al., 2002; Hajjard, Kotchen, 2003; Primatesta, Poulter, 2001; Lloyd-Jones et al., 2005). The reasons for this are unclear, but environmental and therapy factors could be contributing (Wolf-Maier et al., 2003).

The prevalence of AHT in Spain, as well as in other countries, seems to be continuously rising in the last decades (Table 1. and 3.) (Banegas, Rodriguez Artalejo, 2002; Banegas et al., 2002; Hajjard, Kotchen, 2003; Primatesta, Poulter, 2004). The progressive ageing of the population, the current epidemic of obesity and the various treatments available to diagnose and control hypertension and its consequences will probably even more raise the prevalence of AHT in the coming years (Kearney et al., 2005; Lloyd-Jones et al., 2005).

Table 3 Prevalence and management of arterial hypertension in patients aged 60 years and over in the general population of Spain, USA and England based on national data.

	Percentage in period of time	
	1988 - 1991	1999 - 2000
Prevalence in Spain	62%	68%
Prevalence in USA	58%	65%
Prevalence in England	n.a.	81%
Diagnosed in Spain	50%	65%
Diagnosed in USA	68%	70%
Treated in total in Spain	40%	55%
Treated in total in USA	55%	63%
Treated in total in England	n.a.	56%
Controlled AHT in Spain	11%	30%
Controlled AHT in USA	41%	44%
Controlled AHT in England	n.a.	33%
Controlled in total in Spain	5%	16%
Controlled in total in USA	22%	27%
Controlled in England	n.a.	19%

AHT: Arterial hypertension; USA:United States of America; n,a,: data not available
Taken from Banegas JR, Graziani A. 2005..

The available data on the control of AHT come from diverse areas (cross-national surveys, community or population studies, epidemiological research, clinical surveys, etc.), while the most comprehensive information on Spanish situation, as well as in other countries, are from national population surveys.

Specifically, in the general population in Spain the "Hora" study, conducted in 2001 on a representative sample of non-institutionalized population over 59 years of age, reported an AHT control 29.5% in patients treated with antihypertensive drugs.

In the area of primary care the "Prevencat" study, conducted in adults with AHT, hypercholesterolemia or diabetes mellitus (DM) and treated in primary care, reported that only 32.8% of AHT patients were well controlled. The percentage even dropped to 16, 8%

if we consider AHT who had other risk factors (diabetes and hypercholesterolemia) (Álvarez-Sala et al., 2005).

Table 4 Control of risk factors in hypertensive patients in Spain.

Risk factor	Controlled
Hypertension	47% (BP <140/90 mmHg)
Dyslipidaemia	40 % (criteria NCEP / ATP III)
Diabetes	29 % (HbA 1c <7%)

BP: Blood Pressure; NCEP: National Cholesterol Education Program; ATP: Adenosin Triphosphat, HbA1c: Glycated hemoglobin
Taken from Banegas JR, Graziani A. 2005.

Progress in the development of the degree of control of AHT has been remarkable as observed in "Controlpres" studies conducted among the AHT population in primary care and treated with medication in Spain between 1994 and 2003 (Table 5) (Coca Payeras, 2005; Coca Payeras, 2002).

Overall, the data obtained in these studies represent a tripling of AHT control compared to the early nineties.

Table 5 Progress in the control of pharmacologically treated arterial hypertension in Spain in diverse areas.

Population	Year				
	1990	1994	1997	2001	2003
General population (60 – 65 years old)	10%			33%	
Patients in primary care (under 20)		13%	16%	29%	39%
Patients in specialized centers (under 20)				42%	47%

Modified from: Banegas JR, Graziani A. 2005.

Moreover, there are significant variations internationally in odds of AHT control. A publication based on national studies in six European countries, USA and Canada estimated that in the past decade control of AHT in Spain was relatively similar to other European countries, being 8% average for whole Europe, but still far below the USA and Canada, where the average is 23% (Wolf-Maier et al., 2003; Wolf-Maier et al., 2004). Differences between American and European countries are large enough to suggest that treatment of AHT has been pursued more intensively in North America than in Europe. The worse control can also be attributed, in part, with lower therapeutic, pharmacological and non-pharmacological compliance in patients (Banegas, Rodriguez-Artalejo, 2002; Banegas et al., 2002; Márquez et al., 2002).

Among different countries, differences in treatment and awareness of AHT are observed, as summarized in Table 3 (Banegas, Rodriguez-Artalejo, 2002; Banegas et al., 1998; Banegas et al., 2002; Hajjard, Kotchen, 2003; Primatesta, Poulter, 2004).

1.2 Perspectives of future development

According to some studies, the prevalence of AHT will affect 29% of all adults worldwide in 2025, compared to the estimated 26% in 2000 (Kearney et al., 2005). The same forecast estimates that in developed economies (Spain included) the prevalence of AHT (Table 6) is not markedly accelerated.

Table 6 Global burden of arterial hypertension prevalence in the world in 2000 and forecast for 2025, by type of country.

Country	Year 2000		Year 2025	
	Men	Women	Men	Women
Developed countries	37.4%	37.2%	41.6%	42.5%
Developing countries	35.3%	39.1%	39.1%	45.9%
India	20.6%	20.9%	22.9%	23.6%
Latin America and Caribbean	40.7%	34.8%	44.5%	40.2%
Middle East	22.0%	23.7%	24.0%	27.0%
China	22.6%	19.7%	27.7%	27.0%
Rest of Asia and islands	17.0%	14.5%	18.8%	17.1%
Sub-Saharan Africa	26.9%	28.3%	27.0%	28.2%

Taken from Banegas JR, Graziani A. 2005.

There are several ways how to assess AHT control (Banegas, Graciani, 2005). The European guidelines state that, given the continuity of the level of BP to cardiovascular risk, it is appropriate to use a classification term BP without AHT and reduce the interest in achieving tight control of BP (European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension, 2003). Therefore the European guidelines indicate that the real threshold for AHT must be regarded as a flexible, higher or lower depending on total cardiovascular risk profile of each individual. So the definition of high-normal BP (Table 2) includes values that can be considered as "elevated" ("hypertension") in subjects with high risk, or acceptable in individuals with lower risk.

In the same line, Kannel (Kannel, 2000) proposed that subjects with mild AHT (systolic blood pressure of 140-160 mmHg) and two or more risk factors (all irrigation> 15-20% at 10 years), constituting 50% of all isolated systolic hypertensions, the subject

should be considered as controlled, if the risk is lower than expected average risk by age or the overall risk is less than the risk that the subject currently has (Álvarez-Sala et al., 2005).

If the control of AHT and other risk factors would not be improved, the health and the economic burden of cardiovascular, renal and neurological associated diseases will increase substantially in the coming decades due to the aging population and high prevalence of AHT and other risk factors associated with elderly people (Wang, Vasan, 2005; Fuster, 1999).

It has really been made quite some progress in the control of AHT, as has been described, but improvements are still needed in all three areas of 1) awareness, 2) treatment and 3) control of AHT.

Also we must not forget that for the health system to cover the costs involved in coping and management of prevention of AHT, especially primary, budget should be enlarged, because focusing on prevention will save high expenses connected with treating already developed AHT. This primary prevention must also be provided to children and adolescents, as children and youth could benefit too from interventions taken in order to better control their cardiovascular risk factors such as overweight or high BP (Marín et al., 2005; (Krousel-Wood et al., 2004).

1.3 Etiology of essential hypertension

The majority (95%) of uncontrolled AHT diagnosed in clinics or health care facilities in general, have no defined ethiology, are called essential hypertension, also called primary or idiopathic, while only about 5% are secondary, caused by various conditions, where in high frequency are drugs or adverse effects of medication, renovascular diseases, renal failures, pheochromocytoma and hyperaldosteronism.

1.3.1 Gene-environment interaction

BP results from the interaction of genetic and environmental factors, modulating the underlying predisposition due to inheritance and certain factors that occur during fetal maturation.

Essential hypertension is a heterogeneous disorder, in which there may be considerable variations in the participation of the causal factors in different periods and stages of development, and in different individuals.

On the other hand, different epidemiological and family studies indicate that approximately 20 - 40% of the interindividual variation in BP could be genetically determined. Although there is no clear pattern of Mendelian inheritance attributable to a single genetic locus, it has been shown that familial aggregation of AHT, before age 55, the BP elevation is 3.8 times more frequent among individuals with a family history of AHT compared to those who doesn´t (Carretero, Oparil, 2000; Law, Shiell, 1996).

Studies have also shown that low birth weight is associated with an increased risk of AHT and diabetes mellitus (DM), while a delay in growth in fetal life and infancy is correlated with both AHT and with cardiovascular mortality and insulin-dependent diabetes in adulthood. The most likely mechanism is that of congenital oligonefropatia: lower number of nephrons as a result of delayed intrauterine growth, because nephrogenesis occurs mainly in the last 6-8 weeks of gestation and the number of nephrons cannot recover after birth (Gooduer et al., 2007).

The interaction between genetic variations and environmental factors causes the denominated intermediate phenotypes, mechanisms that determine the final phenotype of AHT by cardiac output and total vascular resistance. Intermediate phenotypes include, among others: the autonomic nervous system, the renin-angiotensin system, endothelial factors, vasopressor and vasodepressor hormones, and body fluid volume.

The boundaries between the influence of environment and genes have not been defined clearly, especially with the detection of intrauterine growth retardation as a strong predictive indicator of future AHT development (Law, Shiell, 1996).

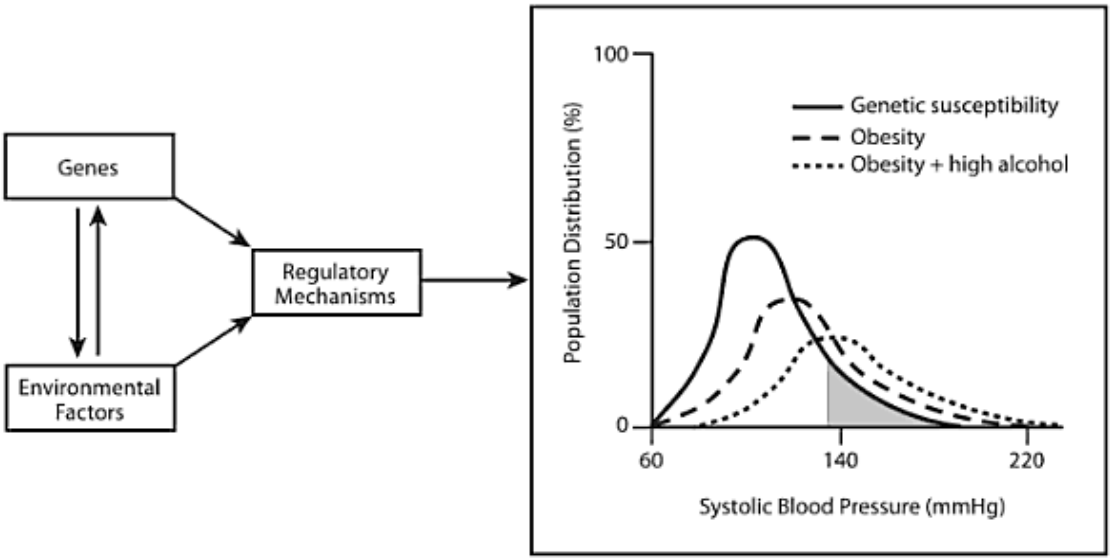

Figure 1 Interaction among genetic and environmental factors in the development of hypertension

The left side of the figure shows that genes and environment interact to affect multiple hypertensive mechanisms. The right side of the figure schematically describes the cumulative effects of genetic and environmental factors on population level BP, which is normally distributed. The solid line shows the theoretic BP distribution caused by genetic susceptibility alone; the shaded area indicates systolic BP in the hypertensive range. Broken lines and dotted lines indicate populations in which on (obesity) or two (obesity and high alcohol intake) environmental factors have been added.
Taken from Kaplan N, 2009.

Family studies have indicated that less than half of the variation in BP in general population is explained by genetic factors. There are many genes that may be involved in the development of AHT. Most of them are involved, directly or indirectly, in the renal re-absorption of sodium (Carretero, Oparil, 2000).

1.3.2 Etiological factors of essential hypertension

It has been described the following factors responsible, among others, for development of hypertension:

- Obesity
- Insulin resistance
- High alcohol intake
- Minerals and vitamins
- Age and Sex

- Sedentary lifestyle
- Stress
- Smoking
- Psychosocial Factors

Many of these factors are additive, and occur with obesity and alcohol intake.

1.3.2.1 Obesity

Obesity has been recognized for a long time as a risk factor for the development of AHT. It is quite prevalent in all developed societies and an increasing frequency among children and youth is observed.

It is known that increased abdominal fat is associated with metabolic consequences and has been associated with dyslipidemia, DM type II and AHT (Blair et al., 1984). The association between hypertension and obesity is a very well established fact, and even though not all obese people develop AHT, it has been found that weight loss, on the other hand, is correlated with a decrease in BP.

Numerous studies have shown a positive correlation between body mass index (BMI) and both systolic and diastolic blood pressure, with stronger correlation in groups of young patients. As mechanisms involved in the relationship are considered: salt sensitivity, since there is evidence suggesting that obesity related AHT is salt-sensitive, and hyperactivity of the sympathetic nervous system (Cusi, Barlassina, Azzani, 1997; Denton, 1997; Geleijinse, Hofman, Witternan, 1997; INTERSALT, 1988).

1.3.2.2 Insulin resistance

Insulin resistance is a metabolic disorder that is manifested by a reduction in glucose utilization in peripheral skeletal muscle.

The fact that certain ethnic groups do not show association between insulin resistance and AHT probably means that genetic mechanisms are involved as environmental phenomena that counteract the influence of insulin.

Not all individuals with insulin resistance are AHT, nor majority of AHT are obese or suffer with insulin resistance, however, both alterations occur together with a much higher frequency than would be expected by chance (Sowers, 2004).

A mechanism that could explain the relationship between insulin resistance and AHT, an association that is also usually accompanied by a higher or lesser degree of obesity, is the sedentary lifestyle. It has been shown that regular exercise helps to all metabolic and hemostatic patients suffering from insulin resistance. It also tends to reverse the abnormal body composition and distribution of fat present in these patients.

The DM and AHT was associated with an elevated frequency, also in individuals with DM, where majority of whom are obese, AHT is more frequent than in non-diabetic obese patients.

The complications of AHT, such as stroke, peripheral vascular disease, heart failure and coronary events, occur in DM patients with higher frequency compared to non-diabetic patients. The DM also increases the risk of premature cardiovascular disease.

1.3.2.3 High Alcohol Intake

In the past two decades, epidemiological studies have established a link between alcohol consumption and AHT in both sexes and for all types of alcoholic beverages (Rayo Llerena, Marín Huera, 1999). Randomized studies have showed that reducing alcohol consumption decreases the levels of BP in AHT patients both on drug treatment, and those who are not treated with drugs (Bellin, Puddey, Burke, 1996).

Excessive alcohol consumption should be considered a possible risk factor for AHT, also is associated with an increase in BP as well as cardiac arrhythmias, dilated cardiomyopathy and hemorrhagic stroke (Bellin, 1995; Bellin, Puddey, 1993; Wannamethee, Shaper, 1996).

Studies suggest, on the other hand, that moderate alcohol consumption protects against coronary artery disease and ischemic stroke. This moderate consumption has an effect on lipids, mainly by raising levels of high density lipoprotein (HDL) and to a lesser extent, decreasing the levels of low density lipoprotein (LDL) (WHO: Global burden of non-communicable diseases, 2006). Mortality from cardiovascular disease is lower in people who drink alcohol moderately (one drink / day for women and up to two drinks per day for men) (O'Keefe et al., 2014; Sacanella et al., 2002; Goldberg et al., 2001).

1.3.2.4 Nutrition

It is a very well established fact, that composition of the diet can affect BP, increasing the risk of prevalence of AHT and, at the same time, different papers (Makrakis,

Zimanyi, Black, 2007) are linking a decrease in BP with a vegetarian diet while responsible for the decline itself has been identified the high-fiber vegetarian diet, low in fat, high in minerals such as potassium and magnesium and low in salt. Possible positive effect of antioxidant vitamins (E, C) has been also investigated, as reflected in different studies (Archives of International Medicine vol.169 No. 7, April 13, 2009).

1.3.2.4.1 Vitamins

Vitamins represent a group of various organic compounds differing from each other in their chemical composition and features. Vitamins are necessary, in small amounts, to perform specific metabolic functions within the cells and to allow the proper body function.

Water-soluble vitamins - vitamin C and B complex, have minimal reservoirs in human body, being excreted by renal filtration, but on the other hand, fat-soluble vitamins A, D, E and K, are being stored in the livers and fatty tissues and thus possessing potential of toxicity and other effect on human organism if excessive amount is absorbed, which is the reason why they are the main focus in this work.

Vitamin A

Vitamin A and its analogues are important regulators of cell proliferation, differentiation and cell apoptosis, further more involved also in immune functions and having the kidneys as the main target organ where they act. The Retinoic acid (RA), a metabolite of vitamin A, is involved in embryonic kidney development by controlling receptor tyrosine kinase, which controls branching morphogenesis and kidney development (Quadro et al., 2005; Moise et al., 2007; Chambon, 1996).

Non physiological levels of vitamin A in pregnant women affect newborn's organogenesis by decreasing the number of nephrons in kidneys, hence predisposing to future development of AHT in adulthood (Quadro et al., 2005).

In rodents, a median vitamin A deficiency is manifested in a 20% reduction in the number of nephrons, whereas in adult humans, the number of nephrons is considered normal ranges from 0.3 to 1.3 million per kidney (Gagnon, Duester, Bhat, 2002; Niederreither et al., 1999). Recent studies indicate that the decrease in nephron number predisposes development of AHT.

The RA regulates nephron mass and therefore its optimal availability during nephrogenesis is essential. RA levels in the embryonic stage are affected by different factors such as maternal nutrition and alterations in retinol metabolism (Makrakis, Zimanyi, Black, 2007; Mendelsohn et al., 1999; Humes, Cieslinski 1992).

In developing countries, where vitamin A intake by the pregnant woman is deficient, it was found that newborns are born with a lower number of nephrons and thus later on higher chance to develop AHT.

Although vitamin A deficiency in developed countries is not common, congenital nephron number varies greatly and this indicates that fetal retinoic acid levels were low due to the variation in the enzymes that convert retinol to retinoic acid. These children thus require more frequent monitoring of BP because they are more predisposed to develop AHT in adulthood (Dupe et al., 2003).

Vitamin A is acquired fetal from the maternal circulation via the placenta. The levels of vitamin A in the mother are influenced by dietary intake of retinoids, where in the diet vitamin A is present as procarotenoides from plants, and retinyl esters from animals.

Recent experiments carried out among pregnant women in Bangalore (India) and Montreal (Canada) in which the levels of vitamin A were compared in circulating concentrations of retinol in mothers and kidney size of their offspring, showed that renal size were lower in the group of Bangalore in the Montreal suggesting that lower level of retinol in Indian pregnant women affected the renal size of their offspring (Gooduer et al., 2007).

With all this, plus a large number of studies that demonstrate the important role of vitamin A in nephrogenesis, it could be said that proper supplementation with vitamin A is crucial in determining the final number of nephrons and, consequently, the possible development of AHT (Merlet-Benichou et al., 1994; Manning, Vehaskari, 2001).

Further studies should be carried out to identify the various enzymes involved in the metabolism of vitamin A (such as RALDH2, which is essential for the fetal synthesis of RA, or cyp26a1, which catabolise the RA), and to clarify the role of these enzymes with relationship between vitamin A, AHT and nephrogenesis (Niederreither et al., 1999; Dupe et al., 2003; Niederreither et al., 2002).

Folic Acid

Folic acid (FA) is a water-soluble vitamin B group vitamin which is necessary for the formation of structural proteins and hemoglobin. Its deficiency in humans is very rare, with the exception of pregnancy, where there is increased demand due to offspring development (Harman, 1956; Mattson et. al., 2002).

During the last decades, the interest in FA was considerably increased after their ability to prevent neural tube defects such as spina bifida was discovered (Cano et al., 2001; Joshi et al., 2001; Mattson et al., 2002).

Today, beneficial effects of FA were extended beyond this condition. Several disorders are considered to be under the influence of folates, such as various cancers, Alzeheimer disease and preeclampsia. It can reduce levels of homocysteine that are produced as a result of auto-oxidation reactions and can also inhibit lipid peroxidation (Joshi et al., 2001).

Thus FA has also antioxidant properties and since AHT is considered as a state of oxidative stress that may contribute to the development of atherosclerosis and induce damage to other organs, the interest in this has increased. Oxidative stress may play an important role in the pathology of essential hypertension. Several studies have demonstrated the beneficial effect of vitamins C and E on BP due to their antioxidant effects and same goes for FA (Cano et al., 2001).

Despite all the above, it is still unclear the role of FA in hypertension. Although the effect on homocysteine levels are the point of many clinical studies, the antioxidant effect is not guaranteed by these and in other studies homocysteine decrease after supplementation with FA is similar to that which was found with others without supplementation.

Moreover, the beneficial effect of FA on oxidative stress in an individual appears regardless of the reduction of homocysteine. This gives strength to the antioxidant effect that has been described in the FA. Therefore it is suggested that its effects can be double. Firstly the antioxidant effect and, secondly, effects on the levels of homocysteine, or even the combination of both (Cano et al., 2001; Joshi et al., 2001; Halliwell, 2000; Mattson et al., 2002; Olszewski, McCully, 1993).

The concentration of homocysteine is affected (increased) by nutritional deficiencies, especially deficiencies of vitamin B12 and FA.

Other studies suggest that nutritional intervention can be a value to consider when increasing the levels of FA and decrease homocysteine levels in the population.

Vitamin B12

Few studies have been conducted on vitamin B12 and AHT and are always in combination with other vitamins and folate, most of them refer to the relationship with serum levels of homocysteine.

As shown in several observational studies, serum levels of homocysteine are associated with cardiovascular risk (Homocysteine Studies Collaboration, 2002; Bazzano et al., 2006; Homocysteine Lowerist Trialists' Collaboration, 1998). A daily supplementation with folic acid, vitamin B6 and / or vitamin B12 may lower homocysteine levels (Bonaa et al., 2006; Lange et al., 2004). Based on these data there are many studies that support the hypothesis that supplementation with folic acid and B vitamins could prevent cardiovascular disease.

However, the more recent publications maintain consistent in the fact, that the supplementation with folic acid and B vitamins is not proven to be effective in preventing cardiovascular disease. Although the combination of FA and vitamin B6 and / or B12 decrease homocysteine levels, it failed in reducing cardiovascular events (Lee et al., 2005; Wald et al., 2006; Bostom et al., 2001).

Vitamin B6 (Piridoxin)

Low levels of vitamin B6 are associated with AHT in both rats and humans. Low levels of calcium in rats and B6 increase BP, but when replaced to normal levels the effect is reduced (Lal, Dakshinamutri, 1995; Yokogoshi, Kobayashi, 1998; Riemers et al. 2001; Kabir, Yamaguchi, Kimura, 1987; Adachi et al., 1988; Kabir, Kimura, 1989).

Therefore, according to these studies (Aybak et al., 1995; Bender, 1999), B6 may have similar multiple antihypertensive effects (in rats and in humans) as the α-agonists, and diuretics. Intakes of vitamin B6 to 200mg/d had no adverse effects and may be beneficial (Bender, 1999; Dakshinamutri, Paulose, Viswanathan, 1990).

Vitamin C

Vitamin C is a water soluble vitamin and potent antioxidant and cofactor of various enzymes such as those involved in lipid and collagen metabolism (Tuomainen, 2009; Steinberg et al., 1989).

Numerous epidemiological, observational and clinical studies have shown that dietary intake of vitamin C or ascorbic acid plasma concentrations in humans is inversely related to BP, diastolic BP and oxidative stress (Ness, Chee, Elliot, 1997; Galley, Thornton, Howdle, 1997; Fotherby et al., 2000; Block et al., 1999; Grossman et al., 2001).

Studies in AHT rats showed a reduction in BP with the administration of vitamin C. Epidemiological studies in humans also showed an inverse association between vitamin C intake and BP (Yoshioka, Aoyama, Matsushita, 1985).

There is a constant increase of evidences that oxidative stress is involved in the pathogenesis of AHT, which is considered, at the same time, one of the most important cardiovascular risk factors (Vaziri, Liang, Ding, 1999; Nayak et al., 2001; Gonick et al., 1997; Vaziri et al., 1997).

As stated, the goal of many studies is to relate the antioxidant effect of vitamins C and E with decreasing BP in AHT patients. Anti-oxidative status increased by supplementation with vitamins C and E in patients with AHT is associated with a decrease in BP. This suggests that intervention with antioxidants may be helpful in the treatment of AHT (Ness, Chee, Elliot, 1997; Galley et al., 1997; Duffy et al., 1999; Footherby et al., 2000; Block et al., 1999; Grossman et al., 2001; Vaziri et al., 1999; Nayak et al., 2001, Tuomainen, 2009).

Different studies show that the oxidation of low density lipoproteins is involved in atherogenesis development and its progression, while experimental studies have shown that it can be reduced by antioxidants. Some population studies also suggest that increased consumption of fruits and vegetables (high in anti-oxidative vitamins) lowers the risk of atherosclerotic vascular disease (Tuomainen, 2009; Steinberg et al., 1989; Gillman et al., 1995; Gale et al., 1995).

Low plasma concentrations of vitamin C are associated with increased carotid atherosclerosis and cumulative risk of myocardial infarction and stroke (Salonen et al.,

1991; Yokoyama et al., 2000), especially in AHT overweight men (Gale et al., 1995; Gey, Stahelin, Eichholzer, 1993).

In a study conducted by Ramón Rodrigo (Rodrigo, 2008) is evidence that oral administration of vitamins C and E in patients with mild to moderate essential hypertension significantly decreases BP by decreasing oxidative status in blood. This study showed that oxidative stress is involved in the pathogenesis of AHT and that increasing the antioxidant status with vitamin C and E in patients with AHT, BP was decreased (Rodrigo, 2008).

In contrast, the lack of antihypertensive efficacy observed in studies which have been used only as a supplement of vitamin C may be due to the pharmacokinetics of vitamin C and/or decreasing its bio availability under conditions of oxidative stress. The antihypertensive effect of vitamin C occurs in concentrations about 10 mmol/l, which is a plasma concentration that is impossible to be obtained by oral administration (Miller et al., 2005; Jackson et al., 1998).

The combination of vitamin C and vitamin E have an antihypertensive effect, probably due to the fact that this combination is reinforcement, a synergy in their individual properties. Oxidative stress and decreased antioxidant capacity are increased in patients with essential hypertension compared with normotensive patients.

Therefore, we can conclude by highlighting the desirability of adding supplementation with vitamins C and E in patients with essential hypertension therapeutic treatment. (Miller et al., 2005; Jackson et al., 1998; Heller, Werner-Felmayer, Werner, 2006; Rodrigo et al., 2007; Simic et al., 2006 ; Lafer et al., 2006 ; Holowatz, Kenney, 2007).

1.1.1.1.1 Other nutritional aspects

The composition of the diet can affect the BP and participates in the prevalence of AHT. Different studies (Archives of International Medicine vol.169 No. 7, April 13, 2009) reflect a decrease in BP levels associated with vegetarian diet and even some showed a significantly higher urinary potassium secretion in patients following omnivorous diet, maintaining potassium.

As responsible for the decline in BP has been registered high fibre content of vegetarian diet, low in fats or high in minerals such as potassium and magnesium.

Regarding often discussed caffeine, it is proven, that it acutely raises BP with peak around one hour after consumption (Bonita et al., 2007; Mort, Kruse, 2008), however it is still uncertain whether it is only temporary or caffeine intake is one of the risk factors of AHT development (Myers, 2004). It was shown that if the caffeine is consumed in coffee, the risk is not increased, on the other hand, if it is consumed in colas (even sugar free), the risk is increased (Winkelmayer et al., 2005).

The reason for this is probably because of protective antioxidants (polyphenols) contained in coffee and not present in colas (Vinson, 2006).

Vitamin D

Vitamin D deficiency can result from a lack of exposure to ultraviolet B (UVB) radiation from the sun, leading to a limitation in its production by the skin. The vitamin D endocrine system regulates about 3% of the human genome. Observational studies suggest that vitamin D is involved in the pathogenesis of cardiovascular disease and AHT. The antihypertensive properties of vitamin D include renal protective effects, suppression of the renin-angiotensin-aldosterone system, direct effects on vascular cells and effects on calcium metabolism, including prevention of secondary hyperparathyroidism.

The results, largely coming from clinical studies, but are not all consistent, favor the hypothesis that vitamin D, in certain quantities, leads to a decrease in blood pressure (Holick, 2007). Randomized, placebo-controlled trials are needed to definitively clarify and specify the role of vitamin D on the blood pressure (Krause et al., 1998).

Although the mechanism of action of vitamin D on vascular tone and BP is not fully known, there are two mechanisms of action taken into consideration, one directly on the membranes of cells and an indirect one on transport, metabolism and excretion of calcium (Hanni et al., 1995)

Vitamin D deficiency affects at least 50% of the world population (Holick, 2007). This pandemia of hypovitaminosis may be due to lifestyle (reducing outdoor activities) and the environment (pollution), factors that reduce exposure to sunlight, which is necessary for the production of vitamin D in the skin. Conditions associated with reduced UVB required to induce the formation of vitamin D, such as high latitude in some countries, dark skin, industrialization or air-pollution have been related to increases in BP (Rostand, 1997).

There is a hypothesis saying that if the low levels of vitamin D are causing BP pressure, then supplementation of this vitamin might decrease it, as antihypertensive effects of vitamin D occur in patients with high BP and vitamin D deficiency and thus vitamin D supplementation may improve AHT (Holick, 2007; Peterlik, Cross, 2005; Holick, 2004).

The hypothesis that UVB exposure induces the production of vitamin D and that this is associated with a decrease in BP was confirmed by a small study of 18 patients with essential untreated AHT (Krause et al., 1998). The results showed that systolic and diastolic BP decreased 6 mmHg after six weeks of UVB irradiation three times a week.

There are several authors who support this theory: (Scragg et al., 2007; Judd et al., 2008; Martins et al., 2007; Hintzpeter et al., 2008; Pasco et al., 2009), while other authors are the questioning the hypothesis (Snijder et al., 2007; Kulah et al., 2007).

The high prevalence of vitamin D deficiency is an important public health issue because vitamin D hypovitaminosis is an independent risk factor of mortality in the general population. A meta-analysis published in 2013 showed that long-term supplementation with vitamin D was associated with a significant reduction in mortality (Zeng et al., 2013). Moreover the insufficiency of vitamin D is associated with increased cardiovascular events, although it remains to be shown whether this association is causal (Pilz et al., 2008; Pilz et al., 2008; Kienreich et al., 2013)

Various clinical studies and molecular studies also associated vitamin D deficiency as a contribution to insulin resistance, which plays an important role in the development of hypertension (Hanni et al., 1995; Boucher, 1998).

In general the evidence of the antihypertensive effects of vitamin D occurs in patients with high BP and vitamin D deficiency, so these patients could benefit from supplementation of vitamin D (Holick, 2007; Peterlik, Cross, 2005; Bouillon et al., 2008; Scragg, Sowers, Bell, 2007; Ferrari et al., 2009; Hathcock et al., 2007; Holick, 2004).

Vitamin E

Vitamin E (α-tocopherol) is a fat soluble vitamin and one of the most important natural antioxidants (Yamashita et al., 1995; Stampfer et al., 1993). It has several cardio protective effects such as reducing oxidative stress causing decreased lipid peroxidation and reserves of glutathion (Lacy, O'Connor, Schmid-Schonbcin, 1998; Russo et al., 1998;

Tagami et al., 1999), increases glucose utilization by insulin and improves endothelial function of vessels (Paolisso et al., 1993; Barbagallo et al., 1999).

The possible involvement of oxidative stress in the development of AHT has been studied in AHT rats and later on also in human, where epidemiological studies proved that vitamin E decreases high BP. These same studies suggest that the antihypertensive effect of vitamin E is the result of its role in reducing oxidative stress (Lacy, O'Connor, Schmid-Schonbcin, 1998; Russo et al., 1998; Noguchi, 2001).

The effect of vitamin E has been investigated by comparing the BP in rats with intake of vitamin E with another group of rats without intake. The results obtained after 10 weeks were that those who were supplemented with vitamin E had lower BP (Lacy, O'Connor, Schmid-Schonbcin, 1998; Tagmi et al., 1999; Yamashita et al., 1995).

Vitamin E acts on the elevation of BP, oxidative stress and on thrombosis (platelet aggregation). Low levels of vitamin E are being associated with episodes of cardiovascular disease, and increased intake of vitamin E is being associated in reducing the risk of heart disease.

In some studies the effect of vitamin E in the modulation of blood pressure and thrombosis in rats was assessed (Noguchi, 2001; Newas, Nawal, 1998). In those studies (Noguchi, 2001; Newas, Nawal, 1998), it is observed that vitamin E has a significant effect on platelet aggregation and BP. The results of these studies indicate that the long term supplementation of vitamin E has beneficial lowering effect on BP and also reduces the tendency to thrombosis.

When taken in combination with other antioxidants (especially vitamin C), it shows a significant BP lowering effect in AHT humans with promising results for further investigation (Galley et al., 1997; Rodrigo, 2008).

It is described, that combination of antioxidant vitamins containing vitamin E, vitamin C, β-carotene, and zinc given to AHT patients for eight weeks has decreased BP and increased nitric oxide metabolites in urine (Varizi et al., 2000).

1.1.1.2 Age and Sex

The prevalence of AHT in men increases progressively until the age of 70 and afterwards, the level is maintained or even slightly decreased. In women the greatest

increase is around the age of 50 and gradually increasing until the age of 80. The prevalence is very high for both sexes in the age of 70 to 80 years old especially because the systolic component.

1.3.2.5 Sedentary lifestyle

Several studies have shown that regular exercise and physical activity are associated with lower levels of BP and lower prevalence of AHT in general. Physical exercise prevents and restores alterations in endothelium-dependent vasodilatation that appear with age (DeSouza, 2000).

Besides the effect on BP, exercise favourably influences certain factors related to ischemic heart disease such as lowering cholesterol and triglycerides, platelet aggregation and weight, increases high density lipoprotein and glucose tolerance.

1.3.2.6 Stress

Stress is a clear stimulator of the sympathetic nervous system. There are studies supporting that people exposed to psychogenic stress may develop AHT more frequently than non-sufferers.

Studies have shown transient endothelial dysfunction possibly leading to further AHT even in healthy young adults, after experiencing mental stress. Those who suffer increased stress are more likely threatened by developing AHT than those without excessive stress, although the stress tolerance and body respond to it differs individually.

The sympathetic nervous system is involved in the early stages of the development of essential hypertension together with hypertensive effects of salt, obesity, sedentary lifestyle and possibly also stress.

1.3.2.7 Smoking

The tobacco can raise, temporarily, BP in approximately 5-10 mmHg (Freestone, Ramsay, 1982; Lecerof et al., 1990). But on the other hand, the chronic use of tobacco was not associated with an increased incidence of AHT. Regular smokers generally have lower levels of BP than non-smokers, which may be related to the lower weight of smokers, as well as vasodilator effect of nicotine metabolites (Kannel, Higgins, 1990).

But, the tobacco should be avoided in the general population and in AHT particularly, since markedly increases the risk of coronary disease and appears to be related

to the progression to renal failure (Kannel, Higgins, 1990; Orth, 2002). Not even speaking about very well-known increased risk of cancer and other diseases.

1.3.2.8 Psychosocial Factors

The distribution of BP in general population is largely influenced by psychosocial factors, establishing an inverse relationship between socioeconomic status and educational level and BP, where lower socioeconomic status and educational level increasing the prevalence of high BP levels achieved in those populations.

This relationship could be explained by the interaction of different dietary factors and differences in lifestyle, continuous exposure to chronic stress, either by social conflict in which the individual is immersed, by the process of cultural development or westernization and by job stress.

1.4 Patophysiology

The BP is the force or the tension exerted by blood against the walls of the vessels. This force is generated by heart in its pumping function, and may be possibly altered by various factors, whereas AHT is clinically defined as persistent elevation of BP above limits considered normal.

In 95% of AHT patients, the ethiology cannot be positively identified (primary hypertension), defined as secondary AHT in those in which the etiology is known (Hajjard, Kotchen, 2003; Carretero, Oparil, 2000).

Although for the essential hypertension there is no trigger factor identified and tends to develop gradually over many years, the most common combination of factors causing the essential hypertension are gene-environment interaction, obesity, insulin resistance, high alcohol intake, lack of minerals and vitamins in diet, age and sex, physical inactivity, stress and smoking (Kaplan, 2009).

On the other hand, speaking about the secondary AHT, which is usually caused by underlying condition, and tends to develop rapidly with even higher BP, usually the trigger is possible to identify and thus curable. Some of the triggers causing secondary

hypertension are: renal diseases, medication, adrenal gland tumor, illegal drugs (such as cocaine) etc.

Systolic blood pressure (SBP) is the effort that makes the heart to pump blood through the vascular system, while diastolic BP indicates the tension of the vessel walls in times of heart break.

BP is the result of cardiac output and peripheral vascular resistance. Each depends on different factors such as blood volume, myocardial contractility and heart rate to cardiac output. Functional vasoconstriction and/or structural medium caliber arteries (resistance arteries) determine the increase in peripheral resistance (Figure I.1).

In different populations, the hypertensive balance between the two factors is shifted either to relatively high levels of cardiac output (although in absolute values is decreased), as in the case of obesity, salt-sensitivity or young, or to the increased resistance, as in the case of long-standing hypertension, severe uncontrolled AHT or elderly.

1.4.1 Determinants of essential hypertension

The fundamental hemodynamic feature of primary hypertension is the persistent increase in vascular resistance that can be achieved through different pathways. These can converge both structural wall thickening and functional vasoconstriction (Kaplan, 2003).

1.4.1.1 Cardiac output

Cardiac output is defined as the volume of blood pumped by heart in one minute. It can be increased by increasing blood volume (preload), by the contractility of the heart or by nerve stimulation and increased heart rate (http://medical-dictionary.thefreedictionary.com/cardiac+output).

Although increased blood volume (preload) can generate pressure, in practice in patients with established hypertension blood volume is usually low. However, relative plasma volume is disproportionately increased for such levels of blood pressure, because there is a quantitative change in the pressure-volume relationship in primary hypertension.

1.4.1.2 Peripheral resistance

Vascular tone is determined by multiple factors: those that produce functional constriction (rennin-angiotensin-aldosterone excess, altered cell membrane, sympathetic nerve hyperactivity, endothelium-derived factors) that cause structural and hypertrophy (excessive rennin-angiotensin-aldosterone activity, alteration of the cell membrane, hyperinsulinemia, endothelium-derived factors).

The primary cause of AHT - increased peripheral resistance, lies in increasing the tone of the distal vascular resistance arterioles, less than 1mm in diameter which is very important in the genesis and maintenance of BP.

The changes in cardiac output and peripheral resistance are dependent on various operating systems related to each other. While some tend to raise levels of BP (adrenergic activity, renin-angiotensin vasoconstrictor prostaglandins, endothelin and atrial natriuretic factor) others tend to diminish (nitric oxide, vasodilator prostaglandins, bradikins etc.) (Table 7).

Table 7 Regulatory systems in blood pressure.

Pressor systems	Depressor systems
Mediators of peripheral vascular resistance	
Increased resistance	Decreased resistance
Angiotensin II Norepinefrin Epinefrin Vasopresin (ADH) Endotelin Eicosanoids: tromboxan a2 Neuropeptide Y	Bradykinin Nitric oxid Atrial natriuretic peptide Prostaglandins Prostacyclins
Mediators of cardiac output	
Increased output	Decreased output
Aldosteron / mineralocorticoids Vasopresin Increased intravascular volume Increased activity of sympathetic nervous system	Haemorrhage Loss of salt and water Intravascular volume depletion

Taken from Douglas JD, Kaine C, 2002.

The sympathetic nervous system is a key mediator of acute changes in BP and heart rate and may also play an important role in the initiation and maintenance of secondary and primary hypertension. The involvement of the sympathetic nervous system in the pathogenesis of AHT is even higher when it coexists with obesity (Kaplan, 2009).

The rennin-angiotensin-aldosterone system (RAAS) plays a major role in regulating BP and is a key mediator of target organ damage, cardiovascular events and progression of renal disease. Regulates peripheral vascular resistance through direct effects of angiotensin II and intravascular volume indirectly through actions both aldosterone and angiotensin II (Kaplan, 2009).

The renal regulation of BP in normal individuals is the dominant mechanism for long-term control of BP. Most authors believe that the mechanism by which the kidney causes AHT is a disorder of salt excretion.

There are several hypotheses to explain this disorder such as low birth weight, congenital fewer nephrons or glomerular filtration area, thus limiting the ability to excrete sodium, with increased BP (Brenner, Anderson, 1992).

Endothelial cells are sensitive to changes in physical and chemical conditions of the environment around them and since AHT causes hemodynamic stress, which can cause changes in the structure and function of the endothelium.

Cardiac output and peripheral resistance causes, at first, functional changes, and structural changes subsequently perpetuate and accentuate the initial functional changes occur at the level of left ventricle, resistance arterioles, microvascular and finally at aorta and great vessels.

1.4.2 Primary prevention

AHT is the second most common form of cardiovascular disease in the general adult population, in which the development may already occur both in childhood and youth. It would be crucial to detect those children or youth in high risk of future high BP in order to be able to perform primary prevention of AHT by modifications of their diet and lifestyle.

Primary prevention should be a major focus in AHT control, not to mention the associated cardiovascular risk factors, which are treatable or influenced, as well as the presence of associated diseases that must also be considered (Whelton et al., 2002).

Primary prevention can be accomplished mainly by reduction of weight in obese, increased physical activity, reduced alcohol intake to less than 20-30 grams per day, healthy low-salt diet, adequate intake of potassium, fruits, vegetables, low-fat dairy products and minimum unsaturated fats.

It has been found that even very modest reductions in BP in the general population have significant public health benefits, as they help to achieve not only a reduction in the incidence of AHT, but also help to control in AHT subjects and prevention of major cardiovascular events and other associated diseases.

Failure in primary prevention results in increased social and health spending of society and, on the other hand, decrease even in modest AHT has important public health benefits (European Society of Hypertension - European Society of Cardiology guidelines for the management of arterial hypertension, 2003; Dickinson et al., 2006).

Finally, as numerous studies showed, the nutrition has a key role on health, specifically vitamins are micronutrients that are essential and necessary perspective and involved in numerous vital functions. Therefore, the objective sought this study relate function fat-soluble vitamins exerted on the AHT.

1.4.3 Blood pressure and cardiovascular risk

The Framingham study (Franklin et al., 1997) was one of the first which tried to determine the relationship between BP and risk of cardiovascular (CV) diseases.

Later on, in 1990s, a meta-analysis in which a total of 420,000 patients were included (with a follow-up between 6 and 25 years) and in which the relationship between diastolic blood pressure (DBP) and the incidence of cerebrovascular (stroke) and coronary heart disease (CHD) accidents was analyzed confirming the existence of a direct association between DBP and CV complications.

From the results of this study it can be concluded, that a persistent elevation of 5 mmHg DBP represents an increased risk of 34 % for stroke and 21 % for CHD. Report noted that BP has a positive relationship with cerebral hemorrhage and thrombotic stroke, while the strength of the association is lower for coronary complications. In relation to other complications such as heart failure (HF) and renal failure (RF), the magnitude of associations with BP is not so evident.

Regarding coronary complications, females tolerate BP higher than males, while the absolute risk of coronary heart disease as well as the absolute benefits of treatment, equal basal levels of BP is higher in men. Treatment of AHT reduces the risk of both failure and delay its development and progression.

A high percentage of patients with different types of renal diseases develop AHT along which, in turn, may worse kidney function. Despite these data, large clinical trials in AHT or isolated systolic hypertension have not shown a significant reduction in renal

events (e.g., need for dialysis, renal transplantation) with the reduction of BP, probably by low incidence of these complications in patients with essential hypertension.

BP, particularly SBP, increases with age and so does the absolute CV risk, regardless of the presence of other risk factors. On the other hand, history of CV disease, especially at an early age is a predictor of CV risk and it should be taken seriously. Also the increase in resting heart rate is associated with increased mortality from CV disease in general and CHD in particular.

The left ventricular hypertrophy is one of the most prevalent among hypertensive cardiac abnormalities in Spain. The VITAE study (Cohen et al., 2007) has shown that over 60 % of hypertensive patients in primary care presents. The left ventricular hypertrophy is an independent CV risk factor that increases the risk of CV complications such as sudden death, angina pectoris and myocardial infarction and congestive heart failure.

Urinary albumin excretion between 30-300 mg/24 hours (microalbuminuria) is a marker for risk of CV complications in AHT patients, although consideration of the microalbuminuria as a predictor of CV risk factor independent of AHT remains controversial.

Finally, it is important to note that both the DM and hypercholesterolemia increase the absolute CV risk in AHT patients, placing those in positions of high risk.

1.4.4 Complications of Hypertension

AHT can cause numerous complications (Table 8), and may promote the development of both ischemic and hemorrhagic lesions. The likelihood of complications increases when other risk factors coexist, especially hyperlipidemia and smoking, so that the effect of the combination of risk factors is not additive or synergistic but multiplier.

For example, a patient with AHT 45 years old, smoking has two times more likehood of complications than the one who does not smoke, and if the patient would also had high cholesterol, the risk would be 5-6 times higher compared to non-smoking and with normal cholesterol levels (www.meditex.es/elmedico/publicaciones/sistole).

Table 8 Complications of arterial hypertension.

Vascular	Fibromuscular hyperplasia. Arteriolar thickening. Intravascular thrombosis. Aneurysms and microaneurysms. Arteriolar necrosis.
Cardiac	Myocardial infarction Angina pectoris. Heart failure. Ventricular hypertrophy. Cardiomyopathy.
Cerebral	Subarachnoid haemorrhage. Cerebral haemorrhage. Strokes.
Peripheral vascular system	Aneurysms. Intermittent claudication.
Renal	Hypertensive nephrosclerosis. Arteriolar necrosis. Renal artery stenosis.

Modified from Kaplan N, 2009.

Thus, in relation to the data on the epidemiology of AHT, primary prevention should be a key point in control of it, not forgetting, of course, that in most cases the AHT will be associated with other CV risk factors that are, in many cases treatable or influenced, and that frequently exist also associated diseases related to these factors that must also be considered.

2. Objectives of the study

The main objective of this study was to determine the possible association between arterial hypertension and the intake of fat-soluble vitamins A, D and E, with the hypothesis that the intake of fat soluble vitamins A, D and E is associated with the prevalence of arterial hypertension.

Specific objectives of this study were:

- to determine the anthropometric characteristics of the hypertensive subpopulation comparing to the non-hypertensive one,
- to determine the relationship between lipid profile, cholesterol and triglycerides and arterial hypertension,
- to determine the association between dietary intakes of protein, carbohydrate and fat diet and arterial hypertension in the study population.

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3. Methods

3.1 Design of the study

We grounded our investigation on the results from the Hortega Study; a two–stage, nested, population-based, epidemiological case-control monitoring pilot study carried out during the period 1997-2002, in a sample of adult population of the province of Valladolid, Spain.

There was randomly selected, using a dump obtained from the 1997 Municipal Census covering our Health Area, 20 % of the population (n = 35,901) and stratified according to the age and sex. People of equal or more than 90 years, non-residents in the province, and those patients with clear cognitive impairment, terminal patients in clinical status and those with marked inability to ambulate were excluded. This selection left a sample of 34,742 people.

Using a uniform age and sex stratified random sampling, representative subsample of the general population on a second mail survey and interview structured face-to-face interview with closed-questions was performed and the final sample for our study was selected (n = 1,514).

3.2 Study population

We started with a sample of 1 514 people in a population aged from 21 to 89 years, of which were 50.3 % women and 49.7 % men. Within this, those individuals who, following the WHO criteria (World Health Organization - International Society of Hypertension: Guidelines for the Management of Hypertension, 1999) to define AHT and its different subtypes (normal BP < 140/90, except diabetes and secondary prevention that requires <135 /85) differed, were diagnosed as having AHT (n = 654; 43.2 %) of those who were not diagnosed (n = 860; 56.8 %).

Also, were selected hypertensive population patients with AHT previously not known, i.e., those that had measured BP in the query who, in the moment of the study had

levels of SBP and higher diastolic the limit values set by WHO for the diagnosis of AHT and had not previously been diagnosed with this disease (n = 278; 18.4 %) (WHO).

We used this population as not being previously diagnosed with AHT has not been implementing any non-pharmacological measures such as the establishment of a specific diet in order to control their BP values.

Finally, both subpopulations were selected from individuals equal or older than 40 years old, giving us 429 non-AHT individuals (controls) (28.3 %), and 246 new AHT patients (cases) (16.2 %) accepted in our study.

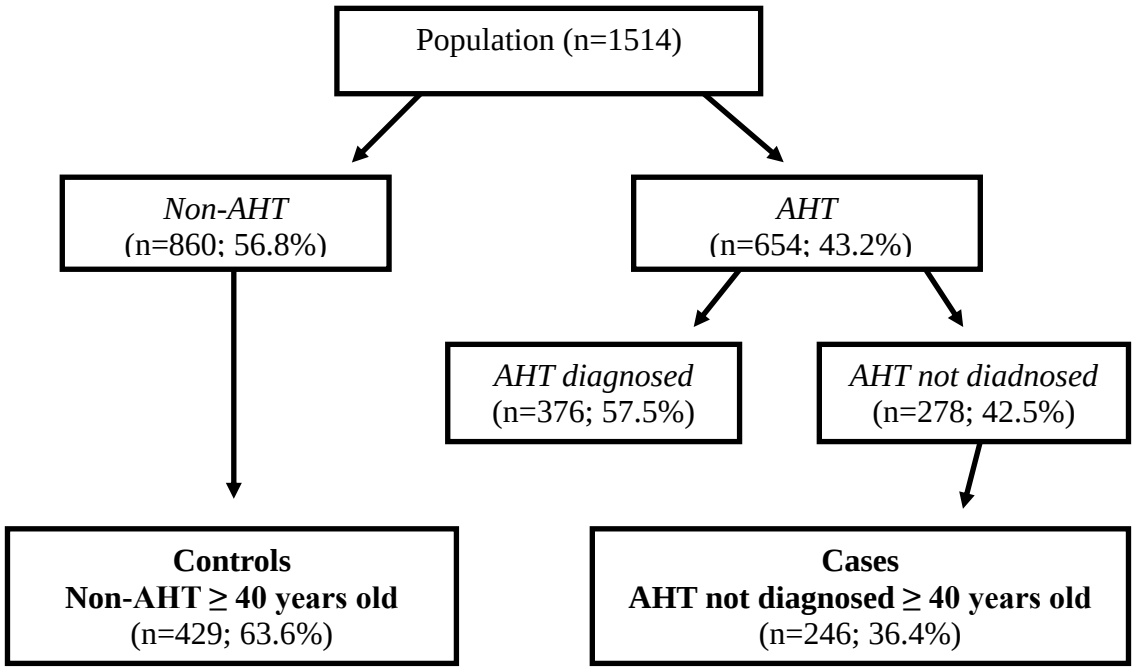

Figure 2 Flow diagram of selection of subpopulations of study

AHT: Arterial hypertension

3.3 Patient data

To carry out the present study an interview where patients consulted their doctor which was performed to one each of the participants, in which they were asked about age, sex, familial status (number of individuals living in the home), level of education, information about employment status (socioeconomic status) and place of residence (rural or urban).

Also series of questions about their health habits, such as doing exercise, and consumption of alcohol and tobacco were raised.

Moreover patients underwent a physical examination in which anthropometric variables (weight, height, waist circumference and hip) were determined. The BP was measured as recommended by the Joint National Committee (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 2003): after at least five minutes at rest, two separate measurements five minutes after each another; or more measurements when the first two readings differed by more than 5 mmHg.

The measurements were performed with automatic monitor OMRON-711 validated and calibrated for this study (Artigao et al., 2000; Foster et al., 1994) following the recommendations of the British Hypertension Society (O'Brien et al., 1993) and Association for the Advancement of Medical Instrumentation (AAMI, 1987) - American National Standard for Electronic or automated sphygmomanometer.

A blood sample for the determination of different biochemical parameters (fasting glucose, triglycerides, HDL-cholesterol, LDL-cholesterol, total cholesterol) was taken and the existence of co-morbidities was assessed by studying patient history.

3.3.1 Evaluation of Daily Intake levels of different components of the diet

Participants in the study underwent a nutritional survey consisting of three 24 hours recalls in three different days, previously validated Food Frequency Questionnaire and photographs of portions collected in order to obtain and assess the intake of various dietary components.

Moreover, the average levels of intake of various dietary components were assessed by the average of the three 24-hours recalls and the semi-quantitative Food Frequency Questionnaire.

The 24-hour recalls were transferred to the program 'Alimentacion y Salud' (Diet and Health) developed by Institute of Nutrition and Food Technology, Universidad de Granada, specifying each food eaten. The program than estimated the respective nutrients.

3.4 Epidemiological analysis

To carry out the analysis of the data a descriptive study of the data using the IBM SPSS software (SPSS, version 17.0; SPSS Inc, Chicago IL) was performed at first, in which the mean values (quantitative variables) and absolute and relative frequencies (qualitative variables) of different variables were calculated, both in the total of the two subpopulations (non-AHT individuals, AHT individuals and newly diagnosed ones), and within each stratifying by sex.

Data were compared by ANOVA (quantitative) and Chi-Square (qualitative) between the two subpopulations (total and by gender). No p value higher than 0.05 was considered significant.

3.4.1 Logistic regression analysis

In a second step, the analytical study of the data was performed through logistic regression analysis in order to estimate a possible association between the presence of hypertension and a certain level of intake of vitamins A, D or E.

Only the role of these vitamins was discussed as considered being fat-soluble, could provide a more accurate correlation between the values of intake and its concentration in the internal environment of the individual. In the case of water-soluble, it is not considered appropriate to evaluate its possible association with the presence of AHT because their concentrations inside the body are always more or less stable despite having a variable intake because its excesses are easily removed by urine.

Thus, the variables of intake of these fat-soluble vitamins are categorized according to whether they met the following conditions:

- reference category or RDI (recommended daily intake) [2/3 of the RDI - RDI],
- lower than recommended value [< 2 / 3 RDI]
- higher than recommended value [> RDI].

Age and sex of the individual was taken into account, since for each age and sex RDI values are different (Table 9).

The estimation of possible association was established on odds ratio (OR c), calculated using bivariate logistic regression, where each of the categories of intake and each of the vitamins, with respect to the reference category, were used.

Furthermore a multivariate logistic regression analysis, by designing a set of adjustment models with different confounding variables included, was conducted by which we calculated the adjusted odds ratio (ORa1, ORa2 and ORa3) for each of the fat soluble vitamins and category (lower RDI or higher RDI).

Thus, in a first step the age, sex and the body mass index (BMI) were included with the variables 'age + sex + BMI'. ORa1: sex + age (every 10 years) + BMI (continuous).

In the next step, co-morbidities, such as the presence or absence of DM and hypercholesterolemia were included in the adjusted model. ORa2: sex + age (every 10 years) + BMI (continuous) + DM (yes/no) + hypercholesterolemia (yes/no).

And finally, in the third step, the model was adjusted to fit the variables: smoking, alcohol intake, exercise performed and energy intake. ORa3: sex + age (every 10 years) + BMI (continuous) + DM (yes/no) + hypercholesterolemia (yes/no) + smoking (smoker/ex-smoker/non-smoker) + alcohol intake (0, > 0 to 5,> 5 to 15,> 15 g of alcohol/day), exercise (METS total continuous) daily energy intake (kcal, continuous).

Table 9 Recommended Daily Intake values of vitamins A, D and E for Spanish population for age and gender.

Gender	Age (years)	*Vitamin A (µg)*	*Vitamin D (µg)*	*Vitamin E (µg)*
Women	40-49	800	5	8
	50-59	800	5	8
	60-69	800	10	8
	≥70	700	15	10
Men	40-49	1000	5	10
	50-59	1000	5	10
	60-69	1000	10	10
	≥70	900	15	12

Taken from: Ortega et al**.:** Recommended daily intakes of energy and nutrients for the Spanish population. Madrid: Department of Nutrition. Universidad Complutense de Madrid; 2004.

3.5 Metabolic Equivalent of Task

One metabolic equivalent (MET) is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 ml O2 per kg body weight x min. The MET concept represents a simple, practical, and easily understood procedure for expressing the energy cost of physical activities as a multiple of the resting metabolic rate. The energy cost of an activity can be determined by dividing the relative oxygen cost of the activity (ml O2/kg/min) x by 3.5 (Jette, Sidney, Blümchen, 1990)

MET is used as a means of expressing the intensity and energy expenditure of activities in a way comparable among persons of different weight. Actual energy expenditure (e.g., in calories or joules) during an activity depends on the person's body

mass; therefore, the energy cost of the same activity will be different for persons of different weight.

The 1 MET reference value of 1 $kcal \cdot kg^{-1} \cdot h^{-1}$, is used by convention and refers to a typical metabolism at rest of an "average" individual. Examples of activities and their METs values are compiled in table 10.

Table 10 Examples of light, moderate and vigorous activities and METs.

Light <3.0 METs	Moderate 3.0–6.0 METs	Vigorous >6.0 METs
Walking slowly = 2.0	Walking very brisk (4mph) = 5.0	Walking/Hiking (4.5mph)= 7.0 Jogging at 6 mph = 10.0
Sitting / using computer = 1.5	Cleaning—heavy = 3.0–3.5 (washing windows, mopping)	Shovelling = 7.0–8.5
Standing—light work = 2.0-2.5 (cooking, washing dishes)	Mowing lawn = 5.5 (walk power mower)	Carrying heavy loads = 7.5
Fishing—sitting = 2.0 Playing most instruments = 2.0–2.5	Bicycling—light effort (10–12 mph) = 6.0 Tennis—doubles = 5.0	Bicycling fast (14–16 mph) = 10.0 Soccer casual = 7.0 Tennis—singles = 8.0

METs are metabolic equivalents. These MET estimates are for healthy adults.

Taken from http://www.hsph.harvard.edu/nutritionsource/mets-activity-table/ (11.12.2013)

4 Results

4.1 General characteristics and anthropometric variables

The Table 11 shows the percentages and mean values concerning general characteristics and anthropometric variables of the total of both subpopulations. In the age group of 40-59 non-AHT individuals subpopulation (64.57 %) is significantly bigger than the AHT (30.08 %), while in the group of individuals from 60-69 years of age the trend reverses and continuing in even higher percentage of AHT patients in group over 70 years old, having only differences statistically significant in the latter case (25.41 % non-AHT versus 56.91 % AHT).

As for the height, weight and BMI mean values are higher and with statistically significant difference for AHT individuals compared to non-AHT. Moreover, although higher than the average value of waist/hip ratio in AHT individuals, no statistically significant differences were obtained.

Table 11 General characteristics and anthropometric variables in populations with hypertension (AHT) and normotensives (non-AHT).

		Non-AHT (n= 429; 63.6%)		AHT (n = 246; 36.4%)	
		N	% / mean ± SD	N	% / mean ± SD
Age	40-59	277	64,57*	74	30,08*
	60-69	43	10,02	32	13,01
	>70	109	25,41*	140	56,91*
Height (cm)		412	162,80 ± 9,00*	239	160,86 ± 10,38*
Weight (kg)		412	69,16 ± 147,23*	240	72,34 ± 13,45*
BMI		427	26,04 ± 3,47*	245	27,97 ± 4,32*
Waist/hip		424	0,87 ± 0,10	240	0,90 ± 0,10

*p-value ≤0.05 (Chi-square; ANOVA test)

AHT: Arterial hypertension; SD: Standard Deviation; BMI: Body Mass Index

4.2 Measurements of blood pressure and biochemical parameters

In the table 12, we observed significant differences between the mean diastolic blood pressure (DBP) and systolic blood pressure (SBP) and between non-AHT and AHT individuals, these values being higher, as might be expected, in the AHT subpopulation (SBP: 121, 01 ± 11, 57 in non-AHT vs. 151, 25 ± 15, 67 in AHT; DBP: 76, 04 ± 7, 28 in non-AHT vs. 87, 21 ± 9, 74 in AHT).

As for triglyceride and fasting glucose, there were also statistically significant differences between the average values of both subpopulations being higher in AHT patients compared to the mean values of non-AHT individuals.

In triglycerides, there were higher values in AHT patients (199, 49 ± 129, 95 mg/dl) compared to the values of the non-AHT patients (175, 97 ± 95, 84 mg/dl). In the fasting

glucose, the data were also significantly higher in AHT patients (96, 51 ± 20, 56 mg/dl) compared to non-AHT ones (90, 49 ± 15, 55 mg/dl).

Finally, the mean total cholesterol, LDL-cholesterol and HDL-cholesterol values were assessed with no statistically significant differences between both subpopulations.

Table 12 Measurements of blood pressure and biochemical parameters of the populations of hypertensive and non-hypertensive individuals.

	Non-AHT (n= 429; 63.6%)		AHT (n=246; 36.4%)	
	N	mean ± SD	N	mean ± SD
Systolic blood pressure (mmHg)	425	121,01 ± 11,57*	244	151,25 ± 15,67*
Diastolic blood pressure (mmHg)	425	76,04 ± 7,28*	244	87,21 ± 9,74*
Triglycerides (mg/dl)	429	175,97 ± 95,84*	246	199,49 ± 129,95*
HDL Cholesterol (mg/dl)	429	52,65 ± 14,40	246	51,60 ± 13,97
LDL Cholesterol (mg/dl)	429	122,38 ± 32,78	246	122,87 ± 34,86
Total Cholesterol (mg/dl)	429	210,23 ± 36,03	246	214,37 ± 39,30
Fasting glucose (mg/dl)	429	90,49 ± 15,55*	246	96,51 ± 20,56*

*p-value ≤0.05 (Chi-square; ANOVA test)

AHT: Arterial hypertension; SD: Standard Deviation; HDL: High Density Lipoproteins; LDL: Low Density Lipoproteins

4.3 Prevalence of co-morbidities

The prevalence of co-morbidities observed in Table 13, showed, with statistically significant differences, higher prevalence of DM (10.2 %), kidney damage (9.4 %), metabolic syndrome (37.8 %), obesity (33.5 %) and overweight (74.8 %) in the subpopulation of hypertensive, compared with non-hypertensive subpopulation, where the prevalence was for DM 3.3 %, kidney damage 2.1 %, metabolic syndrome 15.4 %, obesity 20.6 % and overweight 59.0 %.

While investigating hypercholesterolemia, no significant differences in prevalence were observed between the subpopulations.

Table 13 Prevalence of co-morbidities in total both subpopulations of hypertensive and non-hypertensive individuals.

	Non-AHT (n=429; 63.6%)		AHT (n=246; 36.4%)	
	N	%	N	%
Diabetes mellitus	14	3,3*	25	10,2*
Renal damage	9	2,1*	23	9,4*
Metabolic syndrome	66	15,4*	93	37,8*
Hypertriglyceridemia	216	52,7	109	48,0
Hypercholesterolemia	67	15,7	49	19,9
Obesity	84	20,6*	81	33,5*
Overweight	253	59,0*	184	74,8*

*p-value ≤0.05 (Chi-square; ANOVA test)

AHT: Arterial hypertension; SD: Standard Deviation

4.4 Socio-economic, educational and environmental analysis

As regards the number of cohabitants, no statistically significant differences between the prevalence of AHT and non-AHT populations were found in any of the categories. No statistically significant differences were found either in the variable "residence" comparing rural and urban citizens.

When analysing the variable socio-economic class, statistically significant differences were found in classes II, III and VI.

In the first two classes the percentage in non-AHT subpopulation (15.1 % and 14.8 %, respectively) is higher than their counterparts in the AHT subpopulation (9.1 % and 8.3 %, respectively), whereas in the class VI the trend reverses, and prevalence of AHT is lesser (41.4 %), than non-AHT (56.2 %).

Regarding educational level, only statistically significant differences between the subpopulations were found in the category of "incomplete secondary education", where the prevalence is higher in the AHT population (35.1 %) comparing to the non-AHT (25.0 %).

Table 14 Socio-economic, educational and environmental analysis of subpopulations of hypertensive and non-hypertensive individuals.

		Non-AHT (n=429; 63.6%)		AHT (n=246; 36.4%)	
		N	%	N	%
Nº of cohabitants	none	24	5,7	17	7,1
	1-3	311	73,5	182	75,8
	4 and more	88	20,8	41	17,1
Social-economic class	I	23	5,4	10	4,1
	II	64	15,1*	22	9,1*
	III	63	14,8*	20	8,3*
	IV a	66	15,5	28	11,6
	IV b	15	3,5	11	4,5
	V	18	4,2	15	6,2
	VI	176	41,4*	136	56,2*
Educational level	Illiterate	8	1,9	12	4,9
	Primary school	76	17,9	31	12,7
	Grammar school	47	11,1	20	8,2
	Incomplete secondary school	106	25,0*	86	35,1*
	Vocational school, bachelor	137	32,3	71	29,0
	University studies	50	11,8	25	10,2
Residence	Rural	106	24,7	58	23,6
	Urban	323	75,3	188	76,4

*p-value ≤0.05 (Chi-square; ANOVA test)

AHT: Arterial hypertension; SD: Standard Deviation

4.5 Characteristics of habits

Table 15 results descriptive analysis of the variables related to healthy habits of both studied subpopulations.

Thus, it can be seen that only statistically significant differences between the mean values on cigarettes/day and packs of cigarettes a year were obtained, both being higher in the AHT subpopulation (17, 35 ± 14, 92; 13, 94 ± 24, 89 respectively) comparing the non-AHT (13, 47 ± 10, 41; 9, 63 ± 14, 66).

In terms of grams of alcohol/day consumption, we didn't observe significantly important differences between the subpopulations. No differences were observed either referring to the Metabolic Equivalent of Tasks (METS) per day in all its variations.

Table 15 Characteristics of the habits of hypertensive and non-hypertensive individuals.

		Non-AHT (n= 429; 63.6%)		AHT (n=246; 36.4%)	
		N	% / mean ± SD	N	% / mean ± SD
Smoking habit	Non-smoker	180	42,6	117	48,1
	Smoker	107	25,3	31	12,8
	Ex-smoker	136	32,2	95	39,1
Nº of cigarettes/day		258	13,47 ± 10,41*	133	17,35 ± 14,92*
Packets of cigarettes/year		429	9,63 ± 14,66*	246	13,94 ± 24,89*
Alcohol in grams /day		350	9,91 ± 14,28	210	12,16 ± 20,45
METS walking/day		407	782889,03 ± 770118,11	236	726742,92 ± 624415,01
METS sport/day		108	256307,03 ± 299669,45	45	288897,65 ± 269719,69
METS total/day		409	846740,82 ± 805076,38	236	781829,34 ± 652153,47

*p-value ≤0.05 (Chi-square; ANOVA test)

AHT: Arterial Hypertension; SD: Standard Deviation; METS: Metabolic Equivalent of Tasks

4.6 Dietary components

In the table 16 we can see results of different dietary components analysis, which have been investigated in the two subpopulations, distinguished to macronutrients and

micronutrients, and the latter furthermore between vitamins (water soluble and fat soluble) and minerals.

Overall, no statistically significant differences between the mean values of daily intake among AHT and non-AHT individuals were revealed, except of vitamin B6 intake which in the AHT population had increased level.

However, it should be noted that in most nutrients studied, in average, higher daily dietary intake in AHT individuals was obtained. Only saturated fatty acids, vitamin D, sodium and zinc had the opposite trend.

For fat intake, no significant differences between the two subpopulations were observed, although it is appreciated that the intake of monounsaturated fatty acids (78, 21 ± 34, 30 g in non-AHT; 80, 75 ± 35, 14 g in AHT) is higher than that the intake of saturated fatty acids (56, 11 ± 22, 94 g in non-AHT; 56, 02 ± 21, 85 g in AHT) and intake of these fatty acids to polyunsaturated (26, 75 ± 2, 70 g in non-AHT; 27, 15 ± 12, 24 g in AHT).

Regarding water soluble vitamins (B1, B2, B6, B12, C, niacin and folic acid), only significant differences were found in the mean intake of vitamin B6 in non-AHT (4, 74 ± 1, 73 mg) and AHT (5, 07 ± 1, 72 mg). Also regarding vitamin C, we noted, that its intake was higher than average in both subpopulations.

Regarding the fat-soluble vitamins (A, D and E) no significant differences between the mean values of intake in both studied subpopulation.

Referring minerals, buffers appreciated intake difference between each group analysed, with the increased intake of the potassium, sodium, phosphorus and calcium.

Table 16 Mean values of daily intake of different dietary components of hypertensive and non-hypertensive individuals.

	Non-AHT (n=429; 63.6%)		AHT (n=246; 36.4%)	
	N	mean ± SD	N	mean ± SD
Energetic intake (kcal)	324	4440.52 ± 1580.55	201	4604.96 ± 1581.51
MACRONUTRIENTS				
Proteins (g)	326	228.48 ± 75.76	199	228.41 ± 76.21
Sugars (g)	327	454.93 ± 174.59	198	460.28 ± 166.30
Fats (g)	324	191.15 ± 78.06	201	196.06 ± 77.24
FA monounsaturated (g)	323	78.21 ± 34.30	202	80.75 ± 35.14
FA polyunsaturated (g)	327	26.75 ± 12.70	198	27.15 ± 12.24
FA saturated (g)	326	56.11 ± 22.94	199	56.02 ± 21.85
MICRONUTRIENTS				
Vitamins				
Water soluble				
Vitamin B1 (mg)	324	3.34 ± 1.29	198	3.39 ± 1.25
Vitamin B2 (mg)	325	4.20 ± 3.13	200	4.25 ± 1.68
Vitamin B6 (mg)	327	4.74 ± 1.73*	198	5.07 ± 1.72*
Vitamin B12 (mg)	324	30.54 ± 20.13	201	32.78 ± 21.33
Vitamin C (mg)	324	425.79 ± 235.07	206	427.28 ± 225.05
Niacin (mg)	326	68.90 ± 26.10	199	71.40 ± 25.82
Folic Acid (µg)	320	735.87 ± 314.12	204	752.52 ± 330.70
Fat soluble				
Vitamin A (µg)	320	1655.89 ± 902.81	205	1732.77 ± 962.27
Vitamin D (µg)	325	8.25 ± 9.52	200	8.13 ± 9.71
Vitamin E (mg)	324	18.60 ± 8.20	201	18.79 ± 7.84

Minerals				
Sodium (g)	326	3984.32 ± 1815.18	199	3727.54 ± 1752.95
Potassium (g)	320	6960.04 ± 2668.75	205	7353.34 ± 2697.79
Calcium (mg)	323	1971.93 ± 753.43	202	1995.51 ± 773.97
Phosphorus (mg)	326	2872.24 ± 1064.84	199	2972.32 ± 1071.50
Magnesium (mg)	326	735.63 ± 278.71	199	776.35 ± 273.90
Iron (mg)	320	42.03 ± 370.70	205	44.40 ± 19.65
Zinc (mg)	326	23.94 ± 8.60	199	23.13 ± 7.86
Iodum (µg)	325	198.33 ± 78.50	199	202.31 ± 76.64

*p-value ≤0.05 (Chi-square; ANOVA test)

AHT: Arterial Hypertension; SD: Standard Deviation; FA: Fatty Acids

4.7 Co-morbidities & Vitamins intake

From the results of the table 17, we can clearly see, that non-AHT patients diagnosed with DM have significantly higher intake of vitamin A , comparing to the AHT (2688,55 ± 2065,74 µg vs. 1808,94 ± 820,34 µg), suggesting that higher intake of vitamin A might have protective effects.

As for renal damage, the intake of vitamins was in general higher in AHT subpopulation. Yielding statistically significant differences in case of vitamin E (10,11 ± 7,04 mg vs. 17,56 ± 8,68 mg).

And finally the last statistically significant difference was obtained in the case of obesity where intake of vitamin E was significantly higher in AHT subpopulation (16,24 ± 40,14 µg vs. 7,09 ± 10,80 µg).

The latter two results suggesting possible negative effect of vitamin E intake – contradicting the hypothesis proposed. In all other cases, no statistically significant difference was observed.

Table 17 Intake of vitamins and co-morbidities prevalence analysis.

	Non-AHT (n=429; 63.6%)				AHT (n=246; 36.4%)			
		Vit. A	Vit. D	Vit. E		Vit. A	Vit. D	Vit. E
	N	mean (µg) ± SD	mean (µg) ± SD	mean (mg) ± SD	N	mean (µg) ± SD	mean (µg) ± SD	mean (mg) ± SD
DM	14	2688,55 ± 2065,74*	16,61 ± 50,11	19,73 ± 9,25	35	1808,94 ± 820,34*	32,64 ± 64,98	21,80 ± 7,47
RD	9	868,85 ± 797,70	3,45 ± 3,61	10,11 ± 7,04*	23	2830,17 ± 5826,18	8,47 ± 12,12	17,56 ± 8,68*
MS	66	2617,44 ± 4422,13	12,39 ± 29,83	19,40 ± 10,15	93	2100,90 ± 3068,78	13,14 ± 44,83	18,72 ± 12,86
HTG	216	2327,85 ± 3792,64	11,20 ± 27,83	18,95 ± 10,61	109	2149,84 ± 2876,60	18,01 ± 52,52	19,62 ± 12,32
HCh	67	2170,14 ± 2712,68	10,03 ± 14,22	18,58 ± 11,14	49	2712,68 ± 3997,04	15,67 ± 40,59	20,41 ± 12,22
OB	84	1609,50 ± 2051,38	7,09 ± 10,80*	16,66 ± 8,34	81	2260,91 ± 3711,34	16,24 ± 40,14*	18,17 ± 9,39
OW	253	2200,86 ± 3547,93	11,64 ± 26,03	19,33 ± 10,78	184	2003,96 ± 2575,37	13,74 ± 31,56	18,35 ± 9,91

*p-value ≤0.05 (Chi-square; ANOVA test)

AHT: Arterial hypertension; vit. : vitamin; SD: Standard Deviation; DM: Diabetes mellitus; RD: Renal damage; MS: Metabolic syndrome ; HTG: Hypertriglyceridemia; HCh: Hypercholesterolemia; OB: Obesity; OW Overweight

4.8 Logistic regression analysis

Table 18 presents the results of the logistic regression analysis performed to determine and study the possible association between the intake of fat-soluble vitamins (A, D, E) and the presence of AHT in our study population.

Thus, in a first step odds ratio (ORc) values for each of the intake levels – based on RDI, were calculated, having the category "on RDI" as the reference obtained for each vitamin separately.

In neither cases ORc statistically significant differences in values were obtained, except for the "lower RDI" vitamin D value, where a value of 0.47 (CI 95%: 0.24 to 0.93) was obtained, suggesting that a daily intake less than RDI is negatively associated with the presence of AHT.

Furthermore a multivariate logistic regression analysis, by designing a set of adjustment models with different variables included, was conducted by which we calculated the adjusted odds ratios (ORa1, ORa2 and ORa3) for each of the fat soluble vitamins and category (lower RDI or higher RDI).

Thus, in a first step the age, sex and BMI were included with the variables "age + sex + BMI". ORa1: sex + age (every 10 years) + BMI (continuous).

In the next step, the representative of co-morbidity variables, such as the presence or absence of DM and hypercholesterolemia were included in the adjusted model. ORa2: sex + age (every 10 years) + BMI (continuous) + DM (yes/no) + hypercholesterolemia (yes/no).

In the third step, the model was adjusted to fit the variables: smoking, alcohol intake, exercise performed and energy intake. ORa3: sex + age (every 10 years) + BMI (continuous) + DM (yes/no) + hypercholesterolemia (yes/no) + smoking (smoker/ex-smoker/non-smoker) + alcohol intake (0, > 0 to 5,> 5 to 15,> 15 g of alcohol/day), exercise (METS total, continuous) daily energy intake (kcal, continuous).

The results from logistic regression showed following: ORa1 values obtained in the case of vitamin A very similar to the ORc.

Regarding vitamin D, after including adjusting variables, it is noted that the trend obtained in the bivariate analysis is reversed, with ORa1 above 1, but without statistically significant confidence intervals.

And finally, in vitamin E, we noted that there was a change in the category of "higher RDI", with less than 1, but not statistically significant ORa1.

Thus, in this case, ORa values for both vitamins D to E, no statistically significant confidence intervals obtained are stable. As regards vitamin A, ORa2 value is higher compared to the corresponding ORa1, especially in the category of "higher RDI". In either case, p values less than 0.05 were obtained.

In all cases, the trend for the model of the previous adjustment, except for the category of “lower RDI” vitamin E, wherein the reversed ORa3 value, this being higher than 1 but with confidence interval included 1.

Therefore, based on these results, the possible association between daily intake levels of these vitamins and the presence of AHT is not likely in our study population. Furthermore, when adjusted for the selected variables, no consistent trend is obtained by varying the values of ORa, since in each of the models, vitamins and category values fluctuate independently, even for the same vitamin and the same model. It can be said that the adjustment variables influence variably by category and vitamin.

From the results of nutrition analysis, we can conclude the following: both subpopulations had intake of proteins higher than intake of fat (NHANES II 57 % CH, 25 % fat, 15 % protein). Intake of vitamins in both studied subpopulations was very similar.

Table 18 Analysis of bivariate and multivariate logistic regression.

		RDI	Lower RDI	Higher RDI
Vitamin A	Non-AHT (n (%))	36 (60.0)	34 (63.0)	250 (60.8)
	AHT (n (%))	24 (40.0)	20 (37.0)	161 (39.2)
	ORc (CI 95%)	1.00 (ref)	0.97 (0.57-1.68)	0.88 (0.41-1.88)
	ORa1 (CI 95%)	1.00 (ref)	1.08 (0.59-1.99)	0.91 (0.40-2.07)
	ORa2 (CI 95%)	1.00 (ref)	1.17 (0.63-2.15)	1.80 (0.86-3.74)
	ORa3 (CI 95%)	1.00 (ref)	1.29 (0.65-2.54)	1.55 (0.73-3.31)
Vitamin D	Non-AHT (n (%))	23 (53.5)	180 (57.9)	118 (71.1)
	AHT (n (%))	20 (46.5)	131 (42.1)	48 (28.9)
	ORc (CI 95%)	1.00 (ref)	0.47 (0.24-0.93)*	0.84 (0.44-1.59)
	ORa1 (CI 95%)	1.00 (ref)	1.77 (0.83-3.80)	1.71 (0.83-3.52)
	ORa2 (CI 95%)	1.00 (ref)	1.85 (0.85-4.01)	1.80 (0.86-3.74)
	ORa3 (CI 95%)	1.00 (ref)	1.91 (0.86-4.24)	1.55 (0.73-3.31)
Vitamin E	Non-AHT (n (%))	19 (65.5)	17 (60.7)	240 (66.3)
	AHT (n (%))	10 (34.5)	11 (39.3)	122 (33.7)
	ORc (CI 95%)	1.00 (ref)	0.97 (0.44-2.14)	1.23 (0.42-3.61)

	ORa1 (CI 95%)	1.00 (ref)	0.90 (0.36-2.25)	0.70 (0.20-2.39)
	ORa2 (CI 95%)	1.00 (ref)	0.91 (0.36-2.26)	0.73 (0.21-2.52)
	ORa3 (CI 95%)	1.00 (ref)	1.04 (0.38-2.85)	0.78 (0.22-2.76)

*p-value ≤0.05 (Chi-square)

RDI: Recommended Daily Intake; AHT: Arterial Hypertension; CI: Confidence Interval

5 Discussion

For our epidemiological study we have chosen the case-control design because it has allowed us, using the appropriate statistical tools, assess or estimate the positive or negative association between the various parameters occasion of our study (fat-soluble vitamins) and the development of AHT by calculating odds ratio.

Since the criterion of selection of cases and controls was BP, there are significant differences between groups for both the total sample and in its distribution by sex and age.

From the results obtained in the present study we have not identified positive association between fat-soluble vitamins A, D, E dietary intake, and AHT, although we started with the discrepancy in the results observed in the literature review, clinical trials and studies in experimental animals, discussed in the introduction to this work, which support the involvement of vitamins E and C in decreasing AHT or help in drug treatments for their high antioxidant effect, acting synergistically on oxidative stress present in AHT

Several studies (Holick, 2004; Holick, 2007; Scragg et al., 2007; Hathcock et al., 2007) showed vitamin D deficiency as a parameter to be considered in certain cases of AHT because, as already mentioned in the introduction, the antihypertensive role of vitamin D includes direct effect on cells, vascular effects on calcium metabolism, including prevention of secondary hyperparathyroidism and suppression of renin-angiotensin-aldosterone system.

Since the hypothesis of the association between AHT prevalence and fat-soluble vitamins (A, D and E) intake was proposed in this study, it was decided to control those confounding factors that could have distort the results, which is why we have taken into account the anthropometric measurements, biochemical determinations, pathophysiologic and other factors that helped us to establish and assess the extent of this association.

The results of anthropometric measurements showed that the AHT subpopulation has higher BMI, weight, height, and waist/hip ratio, the latter being more pronounced among AHT women. The positive association between body weight and BP has been also confirmed by the results obtained by the study Intersalt (INTERSALT, 1988).

The control subpopulation (non-AHT) is the majority in the age of 49-59 group, while in AHT subpopulation predominate individuals from group aged over 70 years old, which is a fact confirming increasing BP with progressing age (> 60 % over 60 years), particularly in hypertensive individuals (Rose, 1985), but on the other hand could distort our results.

We observed in this study that the number of cases not diagnosed with AHT in the study population was 18.4 %, a figure that is high and that must be taken into account, given the importance of knowledge and control of AHT in the cardiovascular failure risk prevention. This means, that our study revealed almost 20 % of AHT patients, some of them even suffering with diseases like DM which standing alone require BP monitoring. We should take this information confirming that BP monitoring is not satisfactory and improve it the current situation. Measuring BP as part of pharmaceutical care in pharmacies – healthcare facilities of the first choice, would give pharmacists opportunity to strengthen their position among health sector and make BP measurements more accessible for patients.

The continued growth of obesity in the population, along with the increased number of associated diseases such as DM, dyslipidemia, or CV diseases, established direct relationship with the increase in the prevalence of AHT in society. Therefore, the biochemical measurements were performed, where from the results should be noted that the values of means of triglycerides and fasting glucose are higher in the AHT subpopulation, both of parameters, along with AHT are predictive variables of cardiovascular risk (according to the Spanish Society of Cardiology). As for cholesterol values we found no statistically significant differences between the mean values of this and our subpopulations although both values are higher than recommendation of Spanish Society of Cardiology – 200 mg/dl, (AHT: 210, 23 mg/dl; non-AHT: 214, 37 mg/dl.)

The data on co-morbidity in our population showed that AHT is associated with renal damage, DM and metabolic syndrome, corresponding with conclusions of other AHT prevalence studies in different locations (National Health Survey, Epidemiological Bulletin, Ministry of Health).

As for the intake of macronutrients, which values were obtained by averaging the data from the 24-hour recalls and the semi-quantitative Food Frequency Questionnaire, the

results showed clearly that in the AHT subpopulation consumption of proteins, carbohydrates and fats are higher than in the non-AHT subpopulation, but the differences between them are not statistically significant, so we cannot associate the higher intake of these nutrients to AHT.

One of the limitations of this study is the assessment of nutrients and accuracy of the food intake data, since there is no accurate method developed yet. In our study, in order to limit these, we have used records for three different days, validated questionnaires and used photographs to determine the portion sizes. Furthermore we have used an average from two different methods, as described in the relevant section, and used validated software to transform food intake to nutrients and to calculate the mean values.

As regards the subject of our work, i.e. the association of vitamins A, D and E with hypertension, as already mentioned, we have not found any significant values which would support the hypothesis, since there were no significant differences in the intake of fat-soluble vitamins in hypertensive and non-hypertensive subpopulations.

The literature on vitamin A and AHT study the importance of vitamin A in the genesis of AHT as this vitamin is involved in embryonic development of the kidney and, therefore, the final number of nephrons which, when deficient, may manifest in adulthood as hypertension (Quadro et al., 2005; Moise et al., 2007; Makrakis, Zimanyi, Black, 2007; Dupe et al., 2003). However, we have not found any study on the influence of excess or deficiency of vitamin A intake in the adult population on AHT. From the data obtained in our study population we concluded with the result that we cannot claim this association, as there is no statistically significant difference in the intake of vitamin between the two subpopulations studied.

When we talk about vitamin D, it has also been observed an association between intake and AHT, but no significant differences were found between the mean intake values between the two subpopulations. Keeping in mind that according to the results of the studies and literature reviews speaking about the association between AHT and vitamin D (Krause et al.., 1998; Pilz et al., 2008; Peterlik, Cross, 2005; Bouillon et al., 2008; Scragg et al., 2007) they are referring to the lack, or deficiency of this vitamin in individuals with AHT. In these studies it is noted that the study population is deficient in vitamin D intake and that this supplementation could improve antihypertensive status of these individuals (Holick, 2007; Peterlik, Cross, 2005; Holick, 2004). No negative association between

vitamin D and AHT in individuals in which the plasma concentrations of this vitamin have normal values (40, 00 – 80, 00 ng/ml) is observed (Holick et al. 2011).

In our study, although initially observed a significant odds ratios difference for category "lower RDI", which would mean a negative association between vitamin D and AHT, it has not been confirmed when we calculated adjusted odds ratio. Therefore, no significant association was found in both subsets. Intake of vitamin D in both subpopulations is practically the same in both cases in adjusted RDI mean values, so we can assume that there is no association and, accordingly, should not affect the BP.

Studies on vitamin E and AHT (Miller et al., 2005; Laffer et al., 2007; Holowatz, Kenney, 2007) have been made to associate the antioxidant effect of this vitamin on oxidative stress in AHT, also indicated that low vitamin E levels are associated with CV disease events, and increases in consumption reduces the risk of CHD and associated ones (Ngouchi, 2001; Newaz, Nawal, 1998).

However, this effect is achieved with high levels of vitamin E, which may be toxic (higher 400 IU/day). The combination of vitamin C and E in most studies, due to the synergy between them, reports a reinforcement of their hypotensive effect, decreasing the excess of aldehydes in tissue increased in hypertension, because they protect lipids from peroxidation. If these antioxidant vitamins would be used individually, they would not possess enough antioxidant power to reduce BP in AHT patients, because the concentrations when used individually to exercise their potential antihypertensive effect must be very high concentrations that would potentially become toxic. For this reason in clinical trials supplementation is done with complex vitamins C and E in doses of vitamin C 1g/day with 400 IU/day of vitamin E (Szczeklik et al., 1985; Solzbach et al., 1997; Taddei et al., 1998).

In our population, we observed that the values are within the recommended limits in both subpopulations and no statistically significant differences between the subpopulations were noted to suggest any kind of association, either positive or negative, between the vitamin E intake and AHT. Possibly the association is not observed, because the intake levels in our population is not high enough to enable vitamin E to execute its antioxidant properties and thus reduce AHT.

AHT, as a global problem affecting the public health and also implies high costs for healthcare, needs to be treated effectively and the most effective and also the cheapest approach in this case is prevention. To lower prevalence levels, it is advised to begin by covering primary prevention from an early age, children and adolescents and adult ages (MacMahon, Neal, Rodgers, 2005). Investments in educating population about healthy habits and proper nutrition, heading to the Mediterranean diet, as well as further promotion of importance of daily physical activity and reducing salt intake will be paid back in lowering the cost of treatment of developed AHT and associated diseases.

Finally, we would like to emphasize on the fact that by becoming in many cases, sufficient treatment for preventing or improving the current situation of AHT and being aware that the whole sector must act jointly and not independently, taking into account that in many cases simple change of eating habits and increased physical activity might improve the current situation and thus save further medical expenses.

6 Conclusions

1. This study did not identified any association, neither positive nor negative, between fat-soluble vitamins A, D and E intake and the prevalence of AHT in any of the adjusted odds ratio categories.
2. Patients with newly diagnosed AHT had the same dietary behavior regarding average daily intake of protein, carbohydrates and fats. So we were not able to identify any association between dietary intakes of proteins carbohydrates or fats and AHT in this study.
3. The influence of variables anthropometrics, measured in this study, showed statistically significant positive association with BP values being higher in hypertensive subpopulations.
4. There is no association found between the values of total plasma cholesterol level and the prevalence of AHT in subpopulations, although the mean levels are above the recommendation of the European Society of Hypertension. Triglyceride levels are significantly higher in the hypertensive women subpopulation, but with no significant differences among men subpopulation.
5. There is higher prevalence of DM, kidney damage, metabolic syndrome, obesity and overweight observed in the hypertensive subpopulation with statistically significant differences.
6. In this study we have identified almost 20 % newly diagnosed hypertensives, some of these with comorbidities such as DM, providing evidence of insufficient control of BP – even in patients already suffering with other diseases where BP monitoring is recommended.
7. Results from this study document the importance of pharmaceutical care and need for full implementation of the role of pharmacy as the healthcare facility of choice in monitoring BP as a part of maximization of the effect of pharmacotherapy of diseases such as hyperlipidemia and DM, and wide-range preventive BP screening for early diagnoses.

7. List of abbreviations used in text

AAMI - Association for the Advancement of Medical Instrumentation

AHT - Arterial Hypertension

ANOVA - Analysis of Variance

ATP - Adenosin Triphosphat

BMI - Body Mass Index

BP - Blood Pressure

CHD - Coronary Heart Disease

CI - Confidence Interval

CV - Cardiovascular

DBP - Diastolic Blood Pressure

DM - Diabetes Mellitus

FA - Folic Acid

HbA1c - Glycated hemoglobin

HDL - High Density Lipoproteins

HF - Heart Failure

LDL - Low Density Lipoproteins

METS - Metabolic Equivalent of Tasks

n.a. - not available

NCEP - National Cholesterol Education Program

OR - Odds Ratio

RA - Retinoic Acid

RAAS - Renin-Angiotensin-Aldosterone System

RDI - Recommended Daily Intake

RF - Renal Failure

SBP - Systolic Blood Pressure

SD - Standard Deviation

USA - United States of America

UVB - Ultraviolet B

WHO - World Health Organization

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10. Index of tables

11. Index of figures